Outcome of Right Ventricular Bifocal Pacing in Patients with Permanent Atrial Fibrillation and Severe Dilated Cardiomyopathy Due to Chagas Disease: Three Years of Follow-up

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Summary

Several studies have shown that selected patients with congestive heart failure may benefit from cardiac resynchronization therapy (CRT), which corrects abnormal patterns of left ventricular contraction with biventricular pacing. However, implantation is challenging due to the placement of the left ventricular lead. Recent explorative studies have demonstrated a beneficial effect of right ventricular bifocal pacing, using two leads placed at different positions in the right ventricle, in similar patient populations. The aim of this study was to evaluate the effect of the right ventricular bifocal pacing approach in patients with Chagas disease who have developed both severe dilated cardiomyopathy and chronic atrial fibrillation. In total, 30 patients with a mean age of 52 ± 6 years (16 male, 14 female), atrioventricular block, and New York Heart Association (NYHA) functional class III or IV were included. Patients underwent endocardial, dual-chamber pacemaker implantation with two right ventricular leads, one placed near the right ventricular outflow tract and the other in the apex. Patients were examined by echocardiography, 24-hour Holter ECG, and NYHA class determination before and 3, 6, 12, 18, 24, and 36 months after CRT application. Compared to the baseline, the left ventricular ejection fraction increased significantly in the first months of CRT application, the left ventricular end diastolic diameter decreased significantly, all patients were downgraded to NYHA class I or II, and the incidence of complex ventricular arrhythmias decreased. However, the initial clinical improvement could not be maintained and worsened dramatically after 6 months of CRT. A high mortality rate of 43.3% was observed during the first year, and only 23.3% of patients remained alive after 3 years. At this point, they underwent an electrophysiologic examination, which revealed complex arrhythmias justifying implantable cardioverter defibrillator (ICD) implantation in addition to CRT in six of the patients. In summary, the beneficial effects of right ventricular bifocal pacing could not be maintained beyond the first 6 months of CRT, likely due to the development of severe complex arrhythmias, which is a common part of the natural history of Chagas disease. Therefore, CRT combined with ICD treatment from the outset may be recommended for this patient group.

Key Words

Dilated cardiomyopathy, Chagas disease, atrial fibrillation, cardiac resynchronization therapy, right ventricular bifocal pacing

Introduction

Chagas disease, caused by the protozoa Trypanosoma cruzi, is the most prevalent parasitic infection in Latin America, with approximately more than 16 million carriers [1,2]. Cardiac problems are the most frequent and serious manifestation of chronic Chagas disease, which typically leads to arrhythmias, thromboembolic

phenomena, heart failure, and sudden death [3]. Several studies have shown that selected patients with congestive heart failure could benefit from cardiac resynchronization therapy (CRT), which corrects abnormal patterns of left ventricular contraction with biventricular pacing [4-7]. However, implantation of biventricular pacing systems is challenging due to the placement of the left ventricular lead.

Recent explorative studies have indicated that an alternative CRT approach by means of bifocal ventricular pacing, where two leads are placed at different positions in the right ventricle (mostly in the right ventricular [RV] apex and near the RV outflow tract), may also benefit patients with dilated cardiomyopathy [8,9] as well as patients with chronic Chagas disease who have developed dilated cardiomyopathy [10]. Pachón et al. [11] demonstrated a decrease of the QRS duration, increased cardiac index (cardiac output divided by the body surface area), and an important reduction of mitral regurgitation with bifocal pacing compared to conventional pacing from the RV apex. The objective of the present study was to evaluate the impact of RV bifocal pacing in patients with Chagas disease who have developed both severe dilated cardiomyopathy and chronic atrial fibrillation (AF).

Materials and Methods

The clinical protocol for this single-center, prospective, observational study and the informed consent form were approved by the local ethics review committee. Written informed consent was obtained from each patient prior to study inclusion.

Thirty patients with a mean age of 52 ± 6 years (16 male, 14 female) were enrolled. All patients suffered from Chagas disease, severe dilated cardiomyopathy, and chronic AF with atrioventricular (AV) block, resulting in a mean heart rate of 65 ± 7 bpm. At baseline, 19 patients were categorized in New York Heart Association (NYHA) functional class III and 11 patients in NYHA class IV. None of the patients suffered from any other disease.

Prior to pacemaker implantation, patients were subjected to Doppler echocardiography examination and 24-hour Holter ECG recording. In order to establish bifocal pacing, two leads (Y60BP, Biotronik, Germany) were implanted in the right ventricle. One lead was placed near the RV outflow tract at the interventricular septum and the other in the RV apex

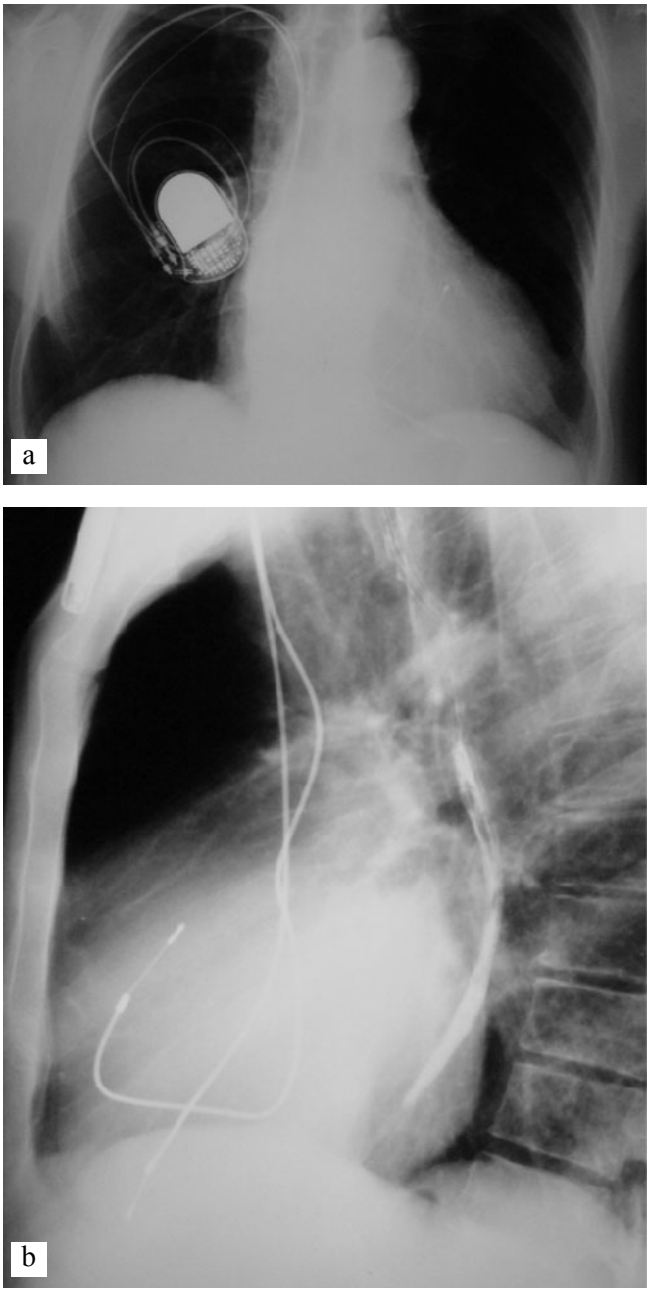

Figure 1. Thoracic X-rays showing the leads implanted in the right ventricle near the outflow tract (panel a) and in the apex (panel b).

(Figures 1a and 1b). The leads were connected to the atrial and ventricular port of a dual-chamber device (Actros DR, Biotronik), which allowed separate testing of pacing and sensing parameters for each of the two leads. The AV delay was set to the lowest value of 10 ms. Sensing values, pacing thresholds, and impedances were recorded, and the output and sensing para-

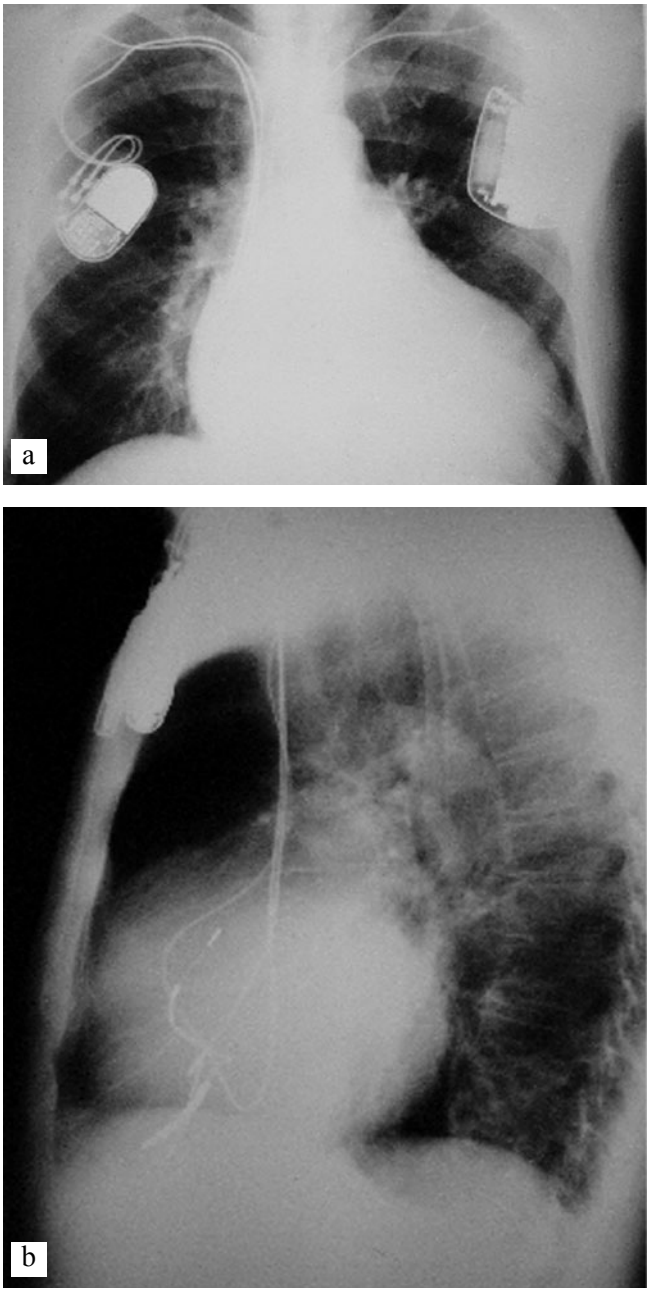

Figure 2. Thoracic X-rays of the bifocal pacing system (panel a) and of the implanted single-chamber ICD (panel b).

meters were adjusted to the patients' individual requirements.

Follow-up examinations took place at 3, 6, 12, 18, 24, and 36 months after CRT application. NYHA class categorization, Doppler echocardiography examination, and 24-hour Holter ECG recording were repeated at each follow-up examination. Sensing values, pacing thresholds, and impedances were recorded, and the output values were optimized at each examination. All diagnostic/statistic values stored in the pacemaker memory between the two examinations were printed out and analyzed.

At the 3-year follow-up, the surviving patients underwent an electrophysiologic examination and some of them received a single-chamber ICD (Microphylax VVI, Biotronik, Germany, Figure 2).

Descriptive data are shown as mean value ± standard deviation. A paired Student's t-test was used to investigate the differences between follow-ups, whereby a p-value < 0.05 was considered significant.

Results

Echo Measurements

Initially, the left ventricular ejection fraction (LVEF) increased significantly from 24% ± 6% before CRT application to 38% ± 10% after 3 months of CRT. However, this was followed by a continuous decline in LVEF during the subsequent follow-ups, decreasing to 12% ± 6% after 36 months (Figure 3). Similarly, the baseline left ventricular end diastolic diameter

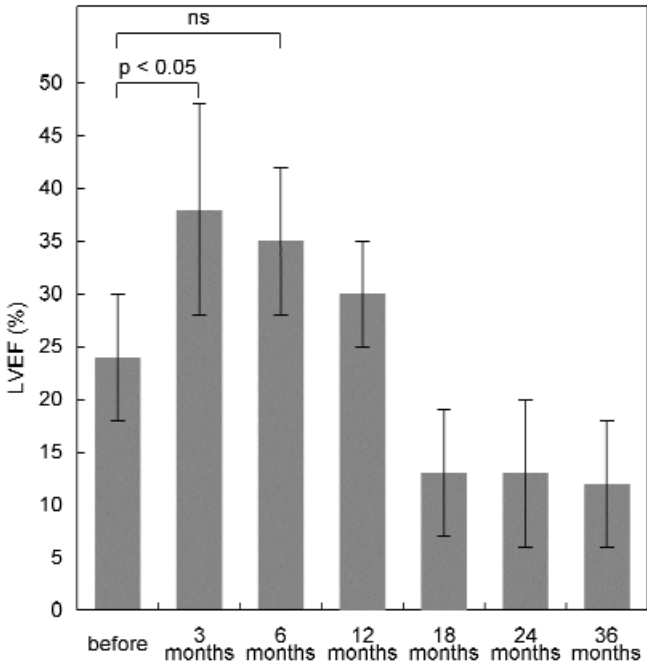

Figure 3. Trend of the left ventricular ejection fraction (LVEF) after CRT application. ns = not significant.

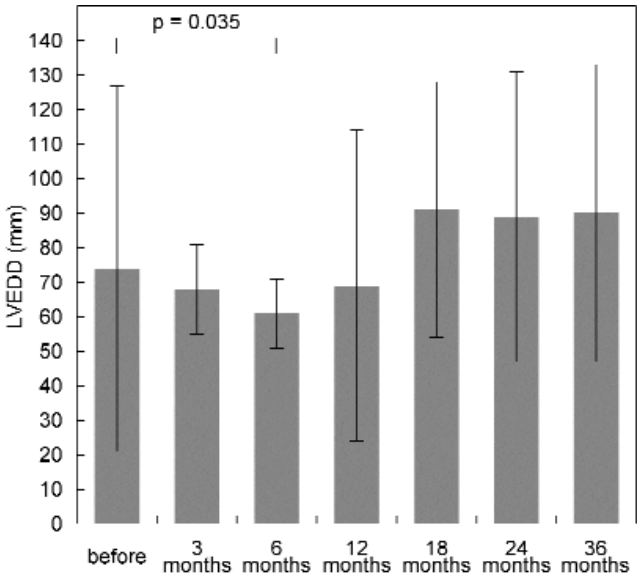

Figure 4. Trend of the left ventricular end diastolic diameter (LVEDD) after CRT application.

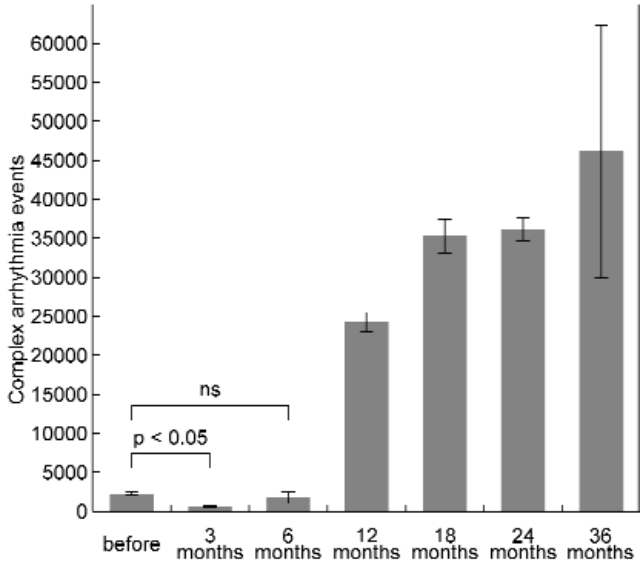

Figure 5. Number of complex ventricular arrhythmias after CRT application. ns = not significant.

(LVEDD) of 74.6 ± 53.0 mm decreased significantly after 6 months of CRT, to 61 ± 10 mm, but it subsequently increased again to beyond the baseline value (Figure 4). No changes were observed in mitral regurgitation.

24-hour Holter ECG

The number of complex ventricular (to be confirmed by author) arrhythmia events after 3 months of CRT decreased significantly compared to the period before the administration of CRT (623 ± 56 vs. 2223 ± 214 counts). However, a dramatic increase in arrhythmic episodes was observed at the 12-month examination (24212 ± 1261 counts), which increased further to 46111 ± 16121 events at the end of the observational period (Figure 5).

NYHA Class

The initial improvement in patients' physical conditions after CRT application was remarkable (Table 1). At the 3-month follow-up, they were in either NYHA class I (17 patients) or NYHA class II (13 patients). However, after the 12-month follow-up, the remaining patients exhibited NYHA class IV symptoms until the end of the study.

Cumulative Survival

Despite a remarkable improvement in NYHA class, echo parameters, and the arrhythmia picture within 6 months of CRT administration, 13 patients (43.3%) died during the first year of CRT. Five additional patients (total 60.0%) died over the course of the second year of CRT and five (total 76.7%) died during the third year of CRT (Figure 6). The causes of cardiovascular mortality are described in Figure 7.

In an effort to improve therapy and cope with a high mortality rate in the setting of a high incidence of complex arrhythmic events documented by 24-hour Holter ECG, the remaining seven patients underwent an electrophysiologic examination at the 3-year follow-up; six of them received a single-chamber ICD. The mean ICD therapy time was 7 ± 3 months, without further deaths. Table 2 summarizes the antiarrhythmic therapies delivered by the implanted ICDs.

NYHA-class	Pre-implant	3 months	12 months	24 months	36 months
I	0	17	0	0	0
II	0	13	0	0	0
III	19	0	0	0	0
IV	11	0	17	12	7

Table 1. Changes in New York Heart Association (NYHA) functional class categorization after CRT application. Number of patients in each class is indicated.

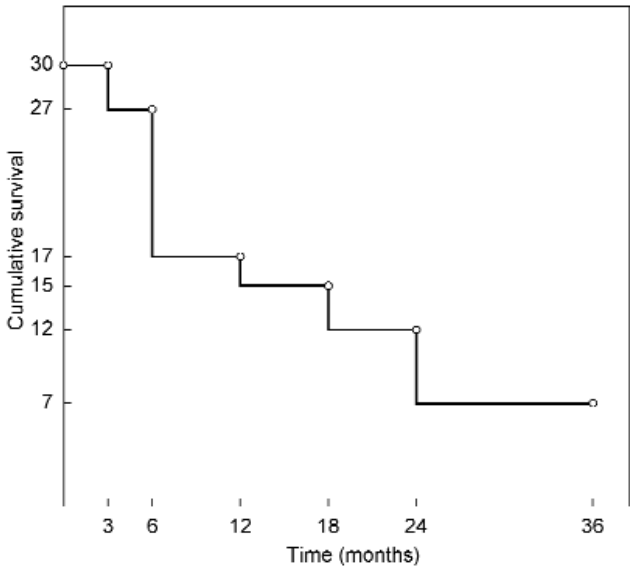

Figure 6. Cumulative patient survival after CRT application.

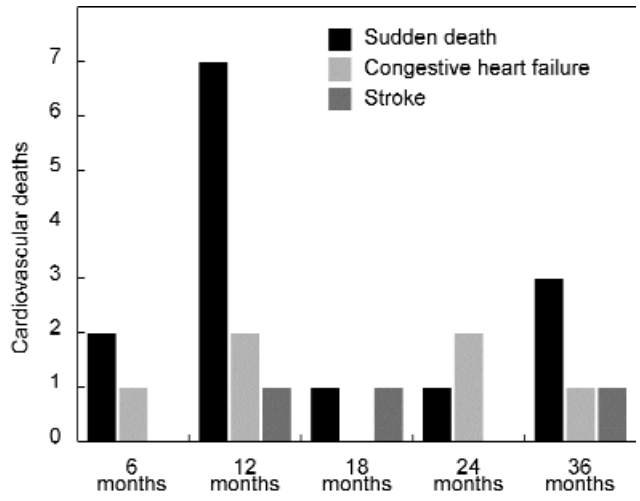

Figure 7. Causes of cardiovascular deaths.

Patient	ATPs (Burst/Ramp)	Shock
1	3	2
2	5	0
3	0	0
4	3	1
5	5	3
6	0	0

Table 2. Overview of antiarrhythmic therapies delivered by the implanted single-chamber ICDs in six patients.

Discussion

In addition to stabilizing the basic heart rate, cardiac pacing is a well-established therapy for dilated cardiomyopathy with congestive heart failure but without bradyarrhythmias. Its main goal is to re-establish electrical and mechanical synchronization of cardiac chambers (atrioventricular, interatrial, interventricular, and intraventricular) and thus restore the pumping potential of the heart. Bakker et al. [12] were the first to observe the benefit of biventricular pacing in NYHA class III and IV patients who suffered from complete left bundle-branch block in the absence of bradyarrhythmia. Subsequently, many studies and trials, e.g., PATH-CHF [13], MUSTIC [14], and Brompton/Harefield [15], demonstrated the benefit of biventricular pacing in treating congestive heart failure. However, left ventricular pacing is associated with some technical difficulties. The endocardial approach involves the coronary sinus and cardiac veins, which is frequently associated with difficulties in assessing the venous system, the need for special leads, a requirement of long-term lead stability, a tendency for higher pacing thresholds, and a risk of phlebitis. Conversely, epicardial pacing typically requires a thoracotomy [11].

We therefore decided to use bifocal RV pacing to achieve intraventricular resynchronization and improve our patients' conditions. In an earlier attempt in five heart failure patients (four with Chagas disease), Páchon et al. found that bifocal RV pacing led to a significant narrowing of the QRS complex, an improvement of all echocardiographic parameters including LVEF, and a reduction in mitral regurgitation [11]. Our study confirmed the potential of bifocal RV pacing to significantly improve echocardiographic parameters in patients with advanced Chagas disease, but it also demonstrated that the benefits of CRT were limited in time. The clinical picture in our patients worsened dramatically after 6 months of bifocal RV pacing, and a high mortality rate was subsequently observed.

The MADIT I [16], MUSTT [17], and MADIT II [18] trials have demonstrated the benefits of ICD therapy in preventing sudden cardiac death, although the population that should receive this therapy is still under discussion. However, two large patients groups who are expected to benefit from prophylactic ICD therapy have been identified: the postmyocardial infarction and the heart failure population [19]. Based on this knowledge and on the large number of sudden cardiac deaths

observed during the course of our study, the seven patients remaining at the 3-year follow-up underwent an electrophysiologic study, which justified implantation of an ICD in six of them.

In summary, the beneficial effect of bifocal RV pacing in patients with advanced Chagas disease could not be maintained beyond the first 6 months of therapy application, likely due to the development of severe complex arrhythmias, which is a common part of the natural history of Chagas disease. Hence, ICD + CRT therapy from the outset appears to be the optimal treatment for this patient group.

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